REMARKS:

The preceding claim amendments and the following remarks are submitted as a full and complete response to the Office Action issued on August 24, 2009. Claims 1 and 3-5 are pending. Claim 1 is amended to incorporate the subject matter of claim 2 and accordingly, claim 2 is cancelled. The amendment of claim 1 is supported by the description at paragraphs 0026 and 0027. No new matter has been added.

I. Rejections of Claims 1-5 under 35 U.S.C. §103(a)

The Patent Office has rejected claims 1-5 under 35 U.S.C. §103(a) as being obvious over Utsumi, et al. (Eur. J. Biochem, 1989, Vol. 181, pp. 545-553) ("Utsumi"), in view of Carter et al. (US 4,483,849)("Carter"), and further in view of Revel et al. (US 4,808,523) ("Revel").

(1) The claimed inventions

Claim 1 is directed to a process for purifying human interferon beta from a recombinant human interferon beta-containing culture comprising performing affinity chromatography and reversed-phase high-performance liquid chromatography (RP-HPLC), wherein the affinity chromatography comprises:

adsorbing the interferon beta-containing culture to an equilibrated affinity chromatography column, followed by washing with an equilibration buffer solution;

washing the column with a washing buffer solution A of pH 6.5-7.5 containing 30-60 wt% of propylene glycol;

washing the column with a washing buffer solution C of pH 6.5-7.5 containing 1-2M NaCl;

washing the column with a washing buffer solution B of pH 6.5-7.5 containing 10-30 wt% of propylene glycol and 1-2M NaCl; and

eluting a human interferon beta-containing fraction with a buffer solution of pH 6.5-7.5 containing 40-60 wt% of propylene glycol and 1-2M NaCl.

Thus, the claimed invention of claim 1 includes three washing steps, that is, washing

with washing buffers A, B and C.

(2) Disclosure of Utsumi

Utsumi discloses a process for purifying interferon beta comprising applying culture fluid containing each mammalian-cell derived recombinant HuIFN-β1 to a column of blue Sepharose CL-6B, eluting with 20 mM phosphate pH 7.4 containing 1M NaCl and 60% ethyleneglycol after washing with 20 mM phosphate pH 7.4 containing 1M NaCl and 30% ethyleneglycol, diluting twofold the obtained eluate from blue Sepharose CL-6B column with water, applying the diluted solution to a column of anti-HuIFN-β1 monoclonal antibody YSB-1, washing and elating the HuIFN-β1 from the column. Further, the obtained solution containing HuIFN-β1 is further purified by RP-HPLC (p.546, 1st column-"Purification of HuIFN- β1s").

However, Utsumi neither discloses three washing steps including washing with washing buffers A, B and C, nor the washing buffers A, B and C per se.

(3) Disclosure of Carter

Carter discloses a process for purifying and stabilizing interferon, comprising the steps of:

adding an interferon-containing fluid to a solid purification matrix;

eluting said interferon from said matrix with a solution containing propylene glycol; and

storing said interferon in a solution containing propylene glycol (claim 1).

Carter also discloses loading interferon to a column equilibrated with a 1 M NaCl/PO4 buffer (E1), *washing with 40% propylene glycol in the 1 M NaCl/PO4 buffer* (E3) and *eluting* with *50% propylene glycol* (Example 1, second paragraph). Specifically, Carter reads: "propylene glycol is more desirable than ethylene glycol in *eluting* interferon from Affi-Gel Blue" (See column 2, lines 30-32) and "Our experiments ...aqueous solutions of 50% propylene glycol have the unique property of stabilizing interferon some 10-fold more than the same solutions lacking propylene glycol" (See

column 2, lines 41-45).

However, it neither discloses three washing steps using washing buffers A, B and C nor the washing buffers A, B and C per se of the claimed invention. Further, it teaches away from the claimed invention since it discloses a solution containing propylene glycol without 1-2M NaCl as an eluting solution. Particularly, it discloses using *50% propylene glycol* which corresponds to the washing buffer A of the claimed invention as an eluting solution.

(4) Disclosure of Revel

Revel discloses *eluting* recombinant interferon β1 from a Blue-Sepharose column with 20mM phosphate buffer pH 7 containing 1M NaCl, and 40% propylene glycol (PG), ultrafiltrating by using a YM10 membrane and concentrating the filtrate, and further purifying the interferon β1 from the concentrated solution by a column of anti-IFN monoclonal antibody (column 13, line 66-column 14, line 8).

However, it neither discloses three washing steps using washing buffers A, B and C nor the washing buffers A, B and C per se of the claimed invention.

(5) Arguments

The claimed method includes three washing steps including washing with washing buffers A, B and C, respectively. According to the method, interferon beta can be purified to a high purity of 99% (see paragraph 0046). This can be achieved because each of the three washing steps removes specific kinds of impurities. That is, the washing with the washing buffer A effectively removes impurities with hydrophobicity, the washing with the washing buffer C removes hydrophilic impurities and the washing with the washing buffer B removes impurity protein (see paragraph 0027 of the specification and FIGS. 3A-3D of the enclosed Experimental Results). In the absence of solution A, the purity of interferon beta remarkably decreases (see paragraph 0041).

Carter neither discloses three washing steps using washing buffers A, B and C nor washing buffers A, B and C per se of the claimed invention. Further, it teaches away from the claimed invention since it discloses a solution containing propylene glycol as an eluting solution. Particularly, it discloses *50% propylene glycol without 1-2M NaCl* which corresponds to the washing buffer A of the claimed invention as an eluting solution. The elution is a process of removing adsorbed *interferon* on the affinity chromatography column into the elution solution, while the washing is a process of removing *impurities* including adsorbed proteins *other than interferon* on the affinity chromatography column into the washing solution. Therefore, a person of ordinary skill in the art would not be motivated to use *50% propylene glycol* as a washing solution because a person of ordinary skill in the art would expect that if it were used as a washing solution, the interferon on the affinity chromatography column would be removed into the washing solution and there would remain no interferon to isolate on the affinity chromatography column. Carter clearly and repeatedly describes using propylene glycol without NaCl as an *elution* solution, instead of as a washing solution, since propylene glycol elutes interferon with a higher yield and stabilizes the purified interferon in an aqueous solution (column 1, lines 35-36, 40-42, column 2, 30-35, Claim 1, line 5-6).

The Examiner asserts that "Because a skilled artisan would know that a washing buffer comprising propylene glycol would stabilize the IFN-*immobilized on the affinity column*, the skilled artisan would be motivated to include a first washing step with a solution comprising propylene glycol for the purpose of protein stabilization, followed by a second washing step comprising washing with the propylene glycol and 1M NaCl solutions taught by Carter and Revel as being useful for washing interferon bound to the affinity column" (page 5, lines 8-12, OA 08/24/2009).

However, neither Carter nor Revel discloses a washing step comprising washing with washing buffer solution B of pH 6.5-7.5 containing 10-30 wt% of propylene glycol and 1-2M NaCl, which allegedly corresponds to the second washing step comprising

washing with the propylene glycol and 1M NaCl solutions referred to by the Examiner. Carter discloses 40% propylene glycol in a 1.0M NaCl/PO4 buffer (E3) used as a washing buffer; however, this buffer does not correspond to the washing buffer solution B of the claimed invention.

Further, a person of ordinary skill in the art would not have used 50% propylene glycol disclosed at Example 1, 2nd paragraph of Carter as a first washing solution since Carter discloses 50% propylene glycol as an *elution* solution and thus, the person of ordinary skill in the art would believe that using this solution as a washing solution would remove the immobilized interferon from the column.

As stated above, the washing is a process of removing impurities including adsorbed proteins *other than interferon* on the affinity chromatography column into the washing solution. Therefore, even though Carter discloses that propylene glycol can stabilize interferon *in an aqueous solution* or *eluted solution*, it does not disclose that propylene glycol can stabilize the IFN-immobilized *on the affinity column* since the washing solution will pass through the column together with the impurities and eventually be discarded.

The Examiner asserts that "even without the specific teachings of Carter regarding the suitability of propylene glycol from a toxicity and protein stabilization standpoint, a person of ordinary skill in the art would have the motivation to optimize the specific conditions for isolation/purification of IFN-β, including the percentage of propylene glycol, and the number of washing steps involved." (Page 5, 2nd and 3rd paragraphs, OA 08/24/2009).

However, the general conditions of the washing methods disclosed by Utsumi, Carter, and Revel are so broad as to encompass a very large number of possible distinct washing methods which are a combination of the number and composition of washing steps. In fact, to derive the washing methods of the claimed invention from the

cited prior arts, one would have to consider *two separate parameters*, that is, the number of washing steps and composition of the washing solution used in each washing step.

Regarding the number of washing steps, Utsumi and Carter disclose only a single washing step and Revel does not disclose a washing step. Thus, none of Utsumi, Carter and Revel disclose the three washing steps with washing solutions A, B and C of the claimed invention. Therefore, there can be an infinite number of optimization ways to select three washing steps of the claimed invention from the cited prior arts. Regarding the composition of each washing step, Utsumi and Carter disclose washing with 20mM phosphate pH 7.4 containing 1M NaCl and 30% ethylene glycol, and 40% propylene glycol in 1.0M NaCl/PO4 buffer (E3), respectively. Thus, none of Utsumi, Carter and Revel disclose the washing solutions A, B and C of the claimed invention. In this regard, there can be an infinite number of optimization ways to select the washing solutions A, B and C of the claimed invention, even if considering that the propylene glycol can stabilize interferon *in an aqueous solution* as disclosed in Carter.

In this regard, even though a combination of three washing steps is selected from the disclosure of Utsumi, Carter and Revel, it would not have been obvious at the time the claimed invention was made to a person of ordinary skill in the art to derive the three washing steps of the claimed invention without undue experimentation since *none of Utsumi, Carter and Revel disclose even a single exact washing step of the claimed invention.*

MPEP 2144.05 states the following: "However, if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus". Id. See also In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); MPEP § 2144.08.

Further, according to MPEP 2144.05, the claimed invention is only obvious if the prior art discloses that the optimized variable is a result-effective variable. MPEP 2144.05 states: "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." (citing In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)).

As stated above, none of the cited prior art recognized that the purity of interferon is a function of the washing steps. None of the cited prior art recognized that the purity of interferon is a function of washing with a washing solution A, washing with a washing solution B and washing with a washing solution C. Regarding the washing solution A, as stated above, Carter only discloses that propylene glycol can elute interferon with a higher yield; however it does not disclose that the purity of interferon can be increased by using propylene glycol as a washing solution. Please note that the purity of interferon can be increased by *selectively* removing impurities, such as adsorbed proteins *other than the interferon* on the affinity column. However, Carter only discloses that propylene glycol can remove *interferon per se*, instead of adsorbed proteins *other than the interferon,* from the affinity column. Regarding the washing solutions B and C, the cited prior art does not disclose the washing solutions B and C per se, let alone that the purity of interferon can be increased by washing with washing solution B and washing with washing solution C. In this regard, we believe that the parameter optimized was not recognized in the art to be a result-effective variable.

Therefore, it would not have been obvious at the time the claimed invention was made to a person of ordinary skill in the art to derive the three washing steps of the claimed invention without undue experimentation since *the parameter optimized was not recognized in the art to be a result-effective variable*.

The applicant encloses herewith the Declaration of Ahn, Jee Won (12 pages) showing unexpected results that the three washing steps of the claimed invention can

increase the purity of interferon in an affinity chromatography.

The Declaration states that in order to identify the effect of propylene glycol and ethylene glycol on the purity of interferon beta, interferon beta was isolated according to a method described in Example 1 of the present application and a method described in Example 1 of the present application except that propylene glycol is replaced with ethylene glycol, and the purity of interferon beta in the finally eluted solution was analyzed by using HPLC. Further, the purity of interferon beta in a solution obtained after each washing step and elution step was analyzed by using HPLC.

As can be shown in FIGS. 1 and 2 of the Experimental Results, interferon beta was eluted at 15 minutes with a single peak in FIG. 1, while there are several peaks around a main peak in FIG. 2, indicating that various impurities are eluted together with the interferon beta. Therefore, the Experimental Results clearly show that the propylene glycol can remarkably increase the purity of interferon beta in the affinity chromatography.

According to FIGS 3A-3D, the purity of the interferon beta remarkably increased by using three washing steps: washing with washing solution A, washing with washing solution C, and washing with washing solution B. Particularly, according to FIG. 3A, washing with washing solution A eluted impurities around 17 minutes and substantially did not elute interferon beta around 15 minutes (see also paragraph 0041 of the specification). This is an unexpected result considering that 50% propylene glycol is used as an elution solution in Carter (see Example 1, 2nd paragraph of Carter). According to FIG. 3B, washing with washing solution C eluted impurities around 11 minutes and substantially did not elute interferon beta around 15 minutes. According to FIG. 3C, washing with washing solution B eluted various impurities around 15 minutes and a small amount of interferon beta around 15 minutes. According to FIG. 3D, eluting the column with the elution solution resulted in the elution of very high purity interferon beta around 15 minutes.

In conclusion, the Experimental Results clearly show the purity of the interferon beta after affinity chromatography remarkably increased by using three washing steps: washing with washing solution A, washing with washing solution C, and washing with washing solution B.

In this regard, it would not have been obvious at the time the claimed invention was made to a person of ordinary skill in the art to derive the claimed invention without undue experimentation.

Accordingly, Applicants respectfully request reconsideration and withdrawal of all the obviousness rejections.

II. Double Patenting

The Patent Office has provisionally rejected claims 1-5 as unpatentable over claims 1-5 of copending Application No. 10/581,597 under obviousness-type double patenting. In view of the provisional nature of this rejection, Applicants will address this rejection once allegedly conflicting claims are in fact patented.

In light of the foregoing, Applicants submit that all outstanding rejections have been overcome, and the instant application is in condition for allowance. Thus, Applicants respectfully request early allowance of the instant application. The Commissioner is hereby authorized to charge any fees or credit any overpayment to Deposit Account No. 02-2135.

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By: _____

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